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INOSITOLS IN POLYCYSTIC OVARY SYNDROME: MECHANISMS, EFFICACY AND SAFETY – A NARRATIVE REVIEW

N. Selvan

Department of Pharmacology, Indira Medical College and Hospitals, Thiruvallur - 631203, Tamil Nadu, India.

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Correspondence to Author:
Dr. Navneeth Selvan

Assistant Professor
Department of Pharmacology,
Indira Medical College and Hospitals,
Thiruvallur - 631203, Tamil Nadu, India.

E-mail: navneeth01@gmail.com

ABSTRACT: Background: Polycystic ovary syndrome (PCOS) is a prevalent endocrine–metabolic disorder characterized by hyperandrogenism, anovulation and heightened cardiometabolic risk. Insulin resistance is central to its pathophysiology. Myo-inositol (MI) and D-chiro-inositol (DCI) are physiological insulin sensitizers increasingly used in PCOS management. **Objective:** To summarize the pharmacology, mechanisms of action, clinical efficacy and safety of inositols in PCOS. **Methods:** A narrative review of randomized trials, mechanistic studies and major reviews on MI and DCI was conducted using PubMed and Scopus. Search terms included "myo-inositol", "D-chiro-inositol", "polycystic ovary syndrome", and "insulin resistance". **Results:** MI, the predominant ovarian isomer, improves insulin signalling, enhances follicle-stimulating hormone responsiveness and supports aromatase activity. DCI predominantly influences metabolic insulin pathways. Clinical evidence shows that MI improves ovulation, menstrual cyclicity, biochemical hyperandrogenism and insulin resistance. The MI:DCI 40:1 combination, reflecting the physiological ovarian ratio, demonstrates superior reproductive and metabolic outcomes. Inositols are consistently well tolerated. **Conclusion:** MI and DCI are safe, evidence-based adjuncts that address both reproductive and metabolic components of PCOS. MI alone or MI:DCI 40:1 represents a rational therapeutic option alongside lifestyle modification and standard pharmacotherapy.

INTRODUCTION: Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders in reproductive-aged women, with an estimated prevalence of 10–15% depending on diagnostic criteria. It is characterised by oligo- or an ovulation, clinical or biochemical hyperandrogenism and polycystic ovarian morphology.

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In addition to reproductive dysfunction, PCOS is strongly associated with metabolic abnormalities such as obesity, dyslipidaemia, impaired glucose tolerance, type 2 diabetes and increased cardiovascular risk [1].

Insulin resistance is central to PCOS pathophysiology. Resulting hyperinsulinaemia stimulates ovarian theca-cell androgen production, decreases sex hormone-binding globulin and exacerbates hyperandrogenism, ultimately impairing follicular development and ovulation [2]. Although conventional therapies including lifestyle modification, metformin, combined oral contraceptives and anti-androgens address discrete components of the syndrome, their efficacy may be

limited by tolerability or incomplete symptom control. Inositols, particularly myo-inositol (MI) and D-chiro-inositol (DCI), have emerged as promising adjunct therapies [3].

These naturally occurring cyclitols act as precursors of inositol phosphoglycans, key second messengers in insulin signalling. Their roles in metabolic regulation and ovarian physiology provide a strong mechanistic basis for their use in PCOS.

Pharmacology of Inositols:

Overview and Biochemical Roles: Inositols are six-carbon cyclohexane polyols involved in membrane structure and intracellular signalling. Of the nine stereoisomers, myo-inositol (MI) and D-chiro-inositol (DCI) are the principal biologically active forms in humans [3]. MI accounts for more than 99% of total body inositol and is highly concentrated in the brain, ovary and endocrine tissues, where it participates in phosphatidylinositol and inositol phosphate signalling pathways [4].

Conversion and Tissue-Specific Distribution: DCI is formed from MI through an insulin-dependent epimerase. DCI-containing inositol phosphoglycans mediate metabolic insulin actions, particularly in the liver and skeletal muscle [4, 5]. In PCOS, defective insulin signalling is associated with reduced epimerase activity, leading to impaired MI-to-DCI conversion and altered tissue-specific MI:DCI ratios [5]. This contributes to insulin resistance in metabolic tissues and relative MI depletion within the ovary.

Physiological Roles in Reproductive and Metabolic Tissues: MI is the predominant isomer in ovarian tissue and is essential for follicle-stimulating hormone (FSH) signalling, aromatase activity and oocyte maturation [7]. DCI, by contrast, has a greater role in hepatic and muscular glycogen synthesis [6]. The complementary roles of MI and DCI provide the rationale for combined therapeutic use in PCOS.

Mechanisms of Action:

Improvement in Insulin Signalling: MI-derived inositol phosphoglycans function as second messengers for insulin, enhancing receptor activation and promoting GLUT-4 translocation to the cell membrane. This increases glucose uptake and improves insulin sensitivity [5]. As insulin levels decline, insulin-mediated stimulation of ovarian theca-cell androgen synthesis decreases, supporting restoration of normal reproductive function [2].

DCI-based phosphoglycans primarily mediate insulin's effects on glycogen synthesis in metabolic tissues [6]. Supplementation with DCI improves glucose disposal, although its influence on reproductive outcomes is modest compared with MI [10].

Regulation of Ovarian Steroidogenesis: MI plays a key role in FSH-mediated follicular development by enhancing FSH signal transduction and aromatase activity, thereby facilitating the conversion of androgens to estrogens [7]. Improved insulin sensitivity further decreases ovarian androgen production, contributing to reduced hyperandrogenism and improved cycle regularity [8, 12].

Restoration of Gonadotropin Imbalance: Women with PCOS frequently exhibit an elevated luteinising hormone (LH) to FSH ratio. Through improvements in insulin resistance and steroidogenesis, MI indirectly supports normalisation of the LH/FSH ratio and helps restore ovulatory cycles [7, 8].

Effects on Oocyte Quality and Assisted Reproduction: MI enhances oocyte cytoplasmic and mitochondrial function, which contributes to improved embryo development. In women with PCOS undergoing *in-vitro* fertilisation (IVF), MI supplementation has been associated with improved oocyte maturation, higher-quality embryos and reduced gonadotropin requirements [13].

Clinical Evidence in PCOS:

Menstrual Cyclicity and Ovulation: Multiple randomized trials using MI at 2–4 g/day demonstrate consistent improvements in ovulation and menstrual regularity. Ovulation is restored in approximately 60–80% of treated women within three to six months [8, 9], and studies such as Papaleo *et al.* report more physiological monofollicular development during induction cycles [12].

Hyperandrogenism: MI reduces total testosterone, androstenedione and DHEAS levels [12, 16], with corresponding improvements in hirsutism and acne,

especially with longer treatment durations [13]. MI is not a replacement for anti-androgens but serves as a well-tolerated adjunct.

Metabolic Outcomes: MI improves fasting insulin, HOMA-IR and lipid parameters across diverse PCOS cohorts [9]. DCI enhances insulin-mediated glucose disposal [6] but may impair aromatase activity at high doses, with potential negative effects on oocyte quality [15]. Thus, DCI is best used in combination with MI.

Fertility and Assisted Reproduction: In IVF/ICSI cycles, MI improves oocyte maturation, embryo quality and reduces gonadotropin requirements [13]. These benefits are clinically relevant given the heightened risk of excessive response in PCOS.

Comparison of Myo-Inositol and D-Chiro-Inositol: MI predominantly supports ovarian functions including FSH signalling, aromatase activity and oocyte maturation [3, 7]. DCI primarily mediates metabolic insulin actions in liver and muscle [4, 6].

Comparative trials indicate that MI has superior effects on ovulation and hormonal parameters, whereas DCI shows limited reproductive benefit [11]. High-dose DCI may reduce aromatase activity and adversely affect oocyte quality [15], making DCI monotherapy inappropriate for women pursuing fertility.

Rationale For The 40:1 Mi:Dci Combination: The physiological ovarian ratio of MI:DCI is approximately 40:1 [14]. In PCOS, this ratio is disrupted due to relative MI deficiency [5], which impairs steroidogenesis and follicular development.

Formulations restoring this physiological ovarian ratio show superior improvements in ovulation, menstrual regularity, androgen levels and metabolic parameters compared with either isomer alone [14]. Therefore, MI monotherapy or MI:DCI 40:1 is preferred over high-dose DCI, especially in fertility-focused care [15, 16].

Safety Profile: Inositols have an excellent safety profile. Across trials, adverse events occur in <5–10% of participants and are typically mild, including nausea, abdominal discomfort and transient gastrointestinal symptoms [9, 17].

No serious drug-related events or clinically relevant drug–drug interactions have been reported. De Leo *et al.* confirm favourable tolerability in gynaecological and obstetric settings, including during preconception and early pregnancy [17]. This safety profile is a significant advantage compared with some conventional pharmacotherapies.

Limitations of Current Evidence: Evidence is limited by modest sample sizes, short treatment durations (commonly 3–6 months) and heterogeneity in PCOS phenotypes, inclusion criteria and outcome measures [18]. Direct comparisons between inositols and other insulin sensitizers are few, and long-term metabolic outcomes, including risk of type 2 diabetes and cardiovascular disease, remain insufficiently studied. Future research should prioritise larger, well-designed trials, phenotype-specific dosing strategies and longer follow-up.

CONCLUSION: MI and DCI are physiologically relevant inositol isomers that exert complementary metabolic and reproductive effects in PCOS. Evidence consistently supports MI, alone or in combination with DCI in a 40:1 physiological ovarian ratio, as an effective and well-tolerated adjunct to lifestyle modification and standard therapy. These agents improve ovulatory function, reduce biochemical hyperandrogenism and enhance insulin sensitivity, with additional benefits in assisted reproduction. Given their favourable safety profile and mechanistic plausibility, inositols provide a rational, patient-friendly therapeutic option, particularly for women seeking fertility or those intolerant to conventional insulin sensitizers.

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